

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year)
13 April 1999 (13.04.99)

International application No.
PCT/US98/14979

Applicant's or agent's file reference
EMU144PCT

International filing date (day/month/year)
20 July 1998 (20.07.98)

Priority date (day/month/year)
19 August 1997 (19.08.97)

Applicant

JOSHI, Harish, C. et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

17 March 1999 (17.03.99)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Christelle Croci

Telephone No.: (41-22) 338.83.38

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JOHN S. PRATT
KILPATRICK STOCKTON LLP
1100 PEACHTREE STREET
SUITE 2800
ATLANTA, GA 30309-4530

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

09 DEC 1999

Applicant's or agent's file reference
EMU144PCT

IMPORTANT NOTIFICATION

International application No.

PCT/US98/14979

International filing date (day/month/year)

20 JULY 1998

Priority Date (day/month/year)

19 AUGUST 1997

Applicant

EMORY UNIVERSITY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

DWAYNE C. JONES

Telephone No. (703) 308-1235

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference EMU144PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/14979	International filing date (day/month/year) 20 JULY 1998	Priority date (day/month/year) 19 AUGUST 1997
International Patent Classification (IPC) or national classification and IPC IPC(6): A01N 43/40, 43/42; C07D 455/04 and US Cl.: 514/321, 320; 546/80		
Applicant EMORY UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

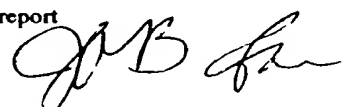
2. This REPORT consists of a total of 4 sheets.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 17 MARCH 1999	Date of completion of this report 01 DECEMBER 1999 
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer DWAYNE C. JONES
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments).*

- ☐ the international application as originally filed.
- ☒ the description, pages (See Attached) , as originally filed.
pages _____ , filed with the demand.
pages _____ , filed with the letter of _____
pages _____ , filed with the letter of _____
- ☒ the claims, Nos. (See Attached) , as originally filed.
Nos. _____ , as amended under Article 19.
Nos. _____ , filed with the demand.
Nos. _____ , filed with the letter of _____
Nos. _____ , filed with the letter of _____
- ☒ the drawings, sheets/fig (See Attached) , as originally filed.
sheets/fig _____ , filed with the demand.
sheets/fig _____ , filed with the letter of _____
sheets/fig _____ , filed with the letter of _____

2. The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)

Claims	<u>1-4</u>	YES
Claims	<u>NONE</u>	NO

Inventive Step (IS)

Claims	<u>1-4</u>	YES
Claims	<u>NONE</u>	NO

Industrial Applicability (IA)

Claims	<u>1-4</u>	YES
Claims	<u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-4 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or provide motivation of the instantly claimed compounds, especially with respect to replacing an ortho methanol moiety for the claimed ortho hydroxy moiety.

_____ NEW CITATIONS _____
NONE

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
pages, 1, 2 and 8-26, as originally filed.
pages, NONE, filed with the demand.
and additional amendments:
Pages 3-7, filed with the letter of 20 October 1999.

This report has been drawn on the basis of the claims,
numbers, NONE, as originally filed.
numbers, NONE, as amended under Article 19.
numbers, NONE, filed with the demand.
and additional amendments:
Claims 1-4, filed with the letter of 20 October 1999.

This report has been drawn on the basis of the drawings,
sheets, NONE, as originally filed.
sheets, NONE, filed with the demand.
and additional amendments:
NONE



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A01N 43/40, 43/42, C07D 455/04	A1	(11) International Publication Number: WO 99/08528 (43) International Publication Date: 25 February 1999 (25.02.99)
(21) International Application Number: PCT/US98/14979 (22) International Filing Date: 20 July 1998 (20.07.98) (30) Priority Data: 60/057,037 19 August 1997 (19.08.97) US (71) Applicant (for all designated States except US): EMORY UNIVERSITY [US/US]; 1380 South Oxford Road, Atlanta, GA 30322 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): JOSHI, Harish, C. [US/US]; 1433 Oak Grove Drive, Decatur, GA 30333 (US). YE, Keqiang [CN/US]; Apartment N12, 2628 Northeast Expressway, Atlanta, GA 30345 (US). KAPP, Judith [US/US]; 411 Chelsea Circle, Atlanta, GA 30307 (US). (74) Agents: PRATT, John, S. et al.; Kilpatrick Stockton LLP, Suite 2800, 1100 Peachtree Street, Atlanta, GA 30309-4530 (US).		(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: NOSCAPINE DERIVATIVES, USEFUL AS ANTICANCER AGENTS (57) Abstract <p>Compounds such as formula (I) are useful in the treatment of tumor cells and the treatment of cancer.</p> <div data-bbox="812 1113 1347 1533"><p style="text-align: right;">(I)</p></div>		

FOR THE PURPOSES OF INFORMATION ONLY

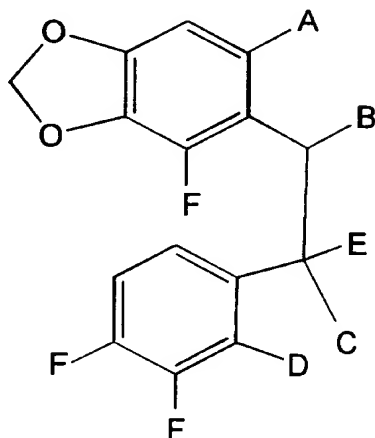
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
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DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

REPLACED BY
ART 34 ANDT

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a compound of the formula



wherein: A is

- (i) $(\text{CH}_2)_1\text{-N}-\text{C}(\text{O})\text{O}-\text{C}_{1-6} \text{ alkyl}$; and W is $\text{C}_{1-6} \text{ alkyl}$;

- (ii) $(\text{CH}_2)_2\text{-N}-$ and forms a six membered ring

with B, said ring containing one nitrogen;

Y is

- (a) $\text{C}_{1-6} \text{ alkyl}$, or H;
- (b) $\text{C}(\text{O})-\text{C}_{1-6} \text{ alkyl}$;
- (c) $\text{CH}_2\text{CH}(\text{OH})\text{-CH}_2\text{-Z}$, wherein Z is $\text{C}_{1-6} \text{ alkyl}$ or $\text{O}-\text{C}_{1-6} \text{ alkyl}$;

- (d) aryl; or
(e) heterocycle;

B is a single bond, OH or halo;

5

C is -OH, -CH₂- or forms a 5-membered lactone or lactam ring with D; and

D is:

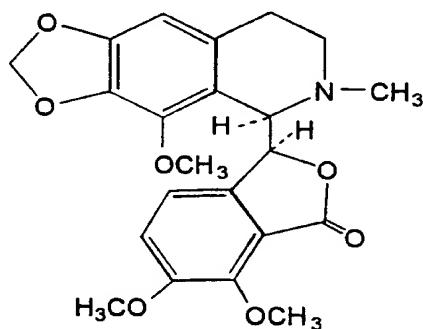
- (i) -OH, -CH₂-halo, -CH(0)-, -COOH, -C(O)-O-C₁₋₆ alkyl, -(CH₂)_n-,
10 -CHOH-, wherein n is an integer and is 1,2, or 3; or
(ii) forms a 5-membered lactone or lactam ring with D;

E is -H or -CH₃; and

F is -OH or -OCH₃,

- 15 or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier,
said composition useful in the treatment of neoplastic diseases,
with the proviso that the formula excludes noscapine of the structure

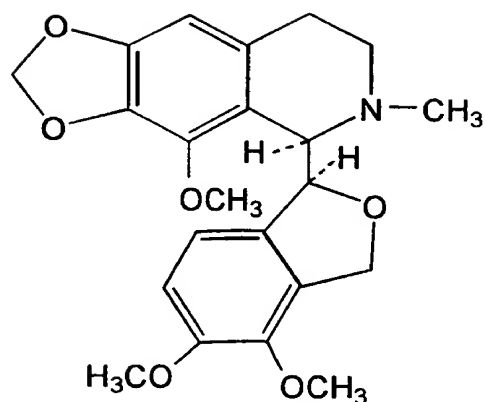
20



25

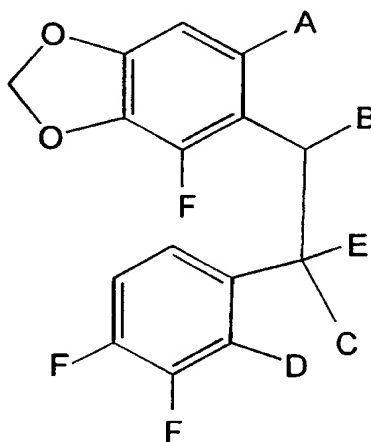
2. The composition of claim 1, wherein the compound is :

29



or pharmaceutically acceptable salt thereof.

3. A method for the treatment of neoplastic diseases, comprising
 5 administering to a mammal in need of such treatment an effective amount of a composition comprising a compound of the formula



10 wherein: A is

- (i) $(\text{CH}_2)_n - \underset{\text{W}}{\underset{|}{\text{N}}} - \text{C}(\text{O})\text{O} - \text{C}_{1-6} \text{ alkyl}$; and W is C_{1-6} alkyl;

15

- (ii) $(\text{CH}_2)_2 - \underset{\text{Y}}{\underset{|}{\text{N}}} -$ and forms a six membered ring

with B, said ring containing one nitrogen;

Y is

- 5 (a) C₁₋₆ alkyl, or H;
(b) C(O)-C₁₋₆ alkyl;
(c) $\text{CH}_2\underset{\text{OH}}{\text{CH}}\text{-CH}_2\text{-Z}$, wherein Z is C₁₋₆ alkyl or O-C₁₋₆ alkyl;
10 (d) aryl; or
(e) heterocycle;

B is a single bond, OH or halo;

15 C is - OH, -CH₂- or forms a 5-membered lactone or lactam ring with D; and

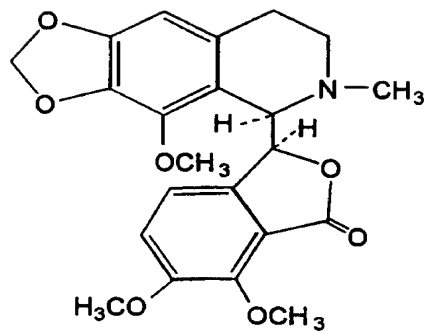
D is:

- (i) -OH, -CH₂-halo, -CH(O)-, -COOH, -C(O)-O-C₁₋₆ alkyl, -(CH₂)_n-,
-CHOH-, wherein n is an integer and is 1,2, or 3; or
20 (ii) forms a 5-membered lactone or lactam ring with D;

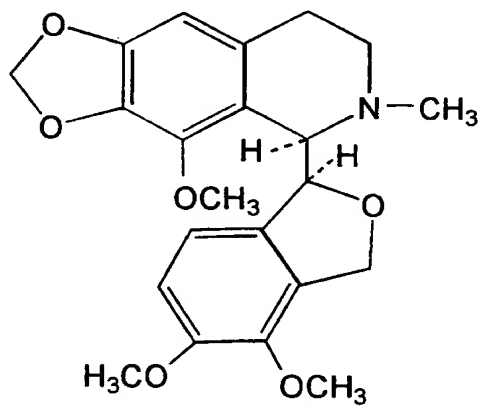
E is -H or - CH₃; and

F is -OH or - OCH₃,

or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier,
25 said composition useful in the treatment of neoplastic diseases,
with the proviso that the formula excludes noscapine of the structure



4. The method of claim 3, wherein the compound is



or pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/14979

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A01N 43/40, 43/42; C07D 455/04

US CL :514/321, 320; 546/80

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/321, 320; 546/80

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

HCAPLUS, REGISTRY, USPATFULL, IFIPAT, HCAOLD structure search with the following terms: harish, kapp, emory, (?neoplas? or ?tumor? or ?tumour? or ?malign?) neoplas?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	Database HCAPLUS on STN, No. 1983:576115, (Inst. Pharm., Univ. Regensburg, Germany) Prior et al., "Borane adducts of narcotine, hydrastine and their reduction products", Arch. Pharm, 316(9), pp. 737-746, 1983.	1 --- 1-2

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

& document member of the same patent family

Date of the actual completion of the international search

09 NOVEMBER 1998

Date of mailing of the international search report

17 DEC 1998

Name and mailing address of the ISA/US
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Box PCT
Washington, D.C. 20231

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